

ABSTRACT

This invention relates to methods and compositions useful for detecting mutations which cause Familial Dysautonomia. Familial dysautonomia (FD; Riley-Day syndrome), an Ashkenazi Jewish disorder, is the best known and most frequent of a group of congenital sensory neuropathies and is characterized by widespread sensory and variable autonomic dysfunction. Previously, we mapped the FD gene, *DYS*, to a 0.5 cM region of chromosome 9q31 and showed that the ethnic bias is due to a founder effect, with >99.5% of disease alleles sharing a common ancestral haplotype. To investigate the molecular basis of FD, we sequenced the minimal candidate region and cloned and characterized its 5 genes. One of these, *IKBKAP*, harbors two mutations that can cause FD. The major haplotype mutation is located in the donor splice site of intron 20. This mutation can result in skipping of exon 20 in the mRNA from FD patients, although they continue to express varying levels of wild-type message in a tissue-specific manner. RNA isolated from patient lymphoblasts is primarily wild-type, whereas only the deleted message is seen in RNA isolated from brain. The mutation associated with the minor haplotype in four patients is a missense (R696P) mutation in exon 19 that is predicted to disrupt a potential phosphorylation site. Our findings indicate that almost all cases of FD are caused by an unusual splice defect that displays tissue-specific expression; and they also provide the basis for rapid carrier screening in the Ashkenazi Jewish population.